Remarks

Claims 10-19, 21, 23-34 and 46-67 were pending in the present application.

Applicants have canceled claims 21, 23, 33, 34, 46, 48, 52, 54, and 61, without prejudice, and amended claims 10-12, 16, 17, 18, 19, 24, 25, 28, 47, 49, 53, 55, 58, 59, and 64, without prejudice. Applicants reserve the right to pursue the deleted subject matter in one or more continuing applications.

The claim amendments have been made to clarify that which Applicants regard as the invention, to correct dependencies, to correct editorial errors and/or to improve clarity. Specifically, claims 10, 17, 24, and 59 have been amended to specify that the at least one inhibitor of free radical oxidation is an EDTA/ethanol combination. Support for this amendment can be found in the specification, for example, at page 9, lines 29-34. Claim 11 has been amended to specify virus concentration. Support for this amendment can be found in the specification, for example, at page 8, lines 10-11. Claims 12, 17, 18, 25, 58, 59 and 65 have been amended to delete unnecessary language, correct editorial errors and/or improve clarity. Claims 16 and 47 have been amended to recite that certain compositions of the invention further comprise histidine. Support for this amendment can be found in the specification, for example, at page 9, lines 29-34. Claims 19 and 53 have been amended to delete formulation numbers which do not contain an EDTA/ethanol combination. Claim 28 has been amended to delete the language regarding total osmolarity as this language is already found in claim 26 (clam 28 is dependent upon claim 27, which is dependent upon claim 26). Claims 47, 49, 53, 55, and 59 have been amended to correct claim dependency in view of the claim amendments. Support for these amendments can be found in the specification, for example, at page 7, lines 8-12, page 9, lines 29-34, page 10, line 21 to page 11, line 4, page 14, lines 1-14, page 15, lines 19-25, page 17, lines 29-32, and page 21, line 29 to page 24, line 16. Claim 64 has been amended to specify that the at least two inhibitors of free radical oxidation is an EDTA/ethanol combination. Support for this amendment can be found in the specification, for example, at page 9, lines 29-34.

No new matter has been added by these amendments.

After entry of the amendments, claims 10-19, 24-32, 47, 49-51, 53, 55-60, and 62-67 will be pending.

Applicants respectfully request entry of the foregoing amendments and consideration of the following remarks.

Double Patenting

Claims 10-18, 21, 24-32, 46-52, 55-60 and 62-67 were provisionally rejected over claims 1-5, 10 and 14 of copending Application No. 11/071,095.

Applicants note that the rejection is provisional and prosecution is ongoing. Applicants respectfully request that the provisional rejection be held in abeyance.

Claim Rejections – 35 U.S.C. § 102

Claims 10-18, 21, 24-32, 46-52, 55-60 and 62-67 were rejected under 35 U.S.C. 102(e) as allegedly being anticipated by Wu et al. (U.S. Patent Application Publication No. 2002/0031527; hereinafter "Wu"). Applicants respectfully traverse.

Independent claims 10, 24, 62, and 64 are distinguished from the teachings of Wu, for example, by providing virus and adenovirus formulations comprising an EDTA/ethanol combination. Dependent claims 16, 17, 32, 47, 59, 62, and 63, and claims dependent thereupon, are further distinguished from the teachings of Wu, for example, by providing virus and adenovirus formulations comprising an EDTA/ethanol combination and histidine.

Wu fails to specifically provide for either ethanol or EDTA, let alone an EDTA/ethanol combination. Wu indicates "antioxidants such as β-mercaptoethanol, DTT, citric acid and the like may also be considered for use in formulations." See Wu, paragraph [0098]. As noted by the Examiner, Wu does not specifically teach the use of EDTA or ethanol. Thus, Wu does not teach each and every element of the claims. See MPEP § 2131.

Wu's speculation concerning possibly using an antioxidant is not a specific disclosure of using a combination of antioxidants such as EDTA and ethanol, but instead references a broad genus. Moreover, Wu does not teach that *any* known antioxidants (such as EDTA and ethanol) can be used to inhibit oxidation. Applicants respectfully submit that the Examiner's use of Evans et al., 2000, J. Pharmaceutical Sci 89:76-87 (hereinafter "Evans") to expand the meaning of the phrase "antioxidants such as β-mercaptoethanol, DTT, citric acid and the like" to inherently

provide for any and all antioxidants, including free radical oxidation inhibitors such as EDTA/ethanol, is inappropriate. An extra reference in a 35 U.S.C. 102 rejection can be "used to explain but not expand the meaning of terms and phrases relied upon as anticipatory of the claimed subject matter." MPEP § 2131.01 (citing *In re Baxter Travenol Labs.*, 952 F.2d 388, 21 USPQ2d 1281 (Fed. Cir. 1991)).

Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 102(e).

Claim Rejections – 35 U.S.C. § 103

Claims 10-19, 21, 23-34, and 46-67 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Wu in view of Evans and Binley et al. (U.S. Patent No. 6,710,173; hereinafter "Binley"). Applicants respectfully traverse.

The teachings of Wu and Evans are discussed above and will discussed further below. Binley is cited by the Examiner as teaching that vaccine combinations comprising replication competent viral vector and DNA plasmids are possible vaccine combinations.

The Examiner contends that it would have been obvious to one of ordinary skill in the art to modify the formulations taught by Wu in order to provide an adenovirus formulation according to the present invention because (1) one would have been motivated to do so given the suggestion by Binley that vaccine compositions can have a combination of replication competent viral vectors and DNA plasmids; and (2) there would have been a reasonable expectation of success given the knowledge of vaccine compositions taught by Binley and given the knowledge that the combination of ethanol and EDTA stabilizes DNA, as taught by Evans.

The claims, as amended, refer to adenovirus and do not mention plasmid DNA. Therefore, as an initial matter, Applicants respectfully point out that Binley is only relevant to claims that require a DNA plasmid, i.e., claims 21, 23, 33, 34, 54, and 61. Since all of these claims have been canceled, the rejection of these claims has been rendered moot. Therefore, Binley will not be discussed further.

Wu and Evans, either alone or in combination, do not provide a suggestion or motivation for a viral formulation comprising an EDTA/ethanol combination. Wu teaches (1) adenovirus formulations that, in a lyophilized formulation, may contain antioxidants such as β-

mercaptoethanol, DTT, citric acid and the like and (2) residual O_2 present during lyophilization leads to oxidation and degradation of proteins. See Wu, paragraph [0098]. Evans teaches that an EDTA/ethanol combination can be used to enhance the stability of plasmid DNA. See Evans, abstract. There is no suggestion or motivation to combine Wu, which is directed to enhancing the stability of adenovirus formulations with antioxidants such as β-mercaptoethanol, DTT, citric acid and the like, with Evans, which is directed to enhancing the stability of plasmid DNA formulations with free radical oxidation inhibitors such as EDTA/ethanol.

Evans' teaching of a beneficial application of an EDTA/ethanol combination for improving DNA stability is not applicable to viral vectors that incorporate DNA. Evans provides no motivation to use an inhibitor of free radical oxidation in a virus formulation because it teaches that such inhibitors improve the stability of plasmid DNA by scavenging free radicals which degrade DNA. It was known that plasmid DNA (composed entirely of DNA) is sensitive to metal ions which catalyze free radical oxidation. See Evans, pg. 80, col. 1, last paragraph. On the other hand, viruses are composed of protein with the DNA or RNA genome located in the capsid, protected from direct free radical attack. Since the genetic material of the virus is protected by the capsid, Evans' teachings concerning plasmid DNA is not sufficient to direct the skilled artisan to use an EDTA/ethanol combination to improve the stability of viral DNA or RNA within a virus.

Furthermore, Wu teaches away from using an EDTA/ethanol combination in an adenovirus formulation. There are different types of oxidation reactions and the use of an inhibitor of one type of oxidation reaction does not provide any suggestion or motivation for the use of an inhibitor of another type of oxidation reaction. Wu teaches that residual O_2 leads to degradation of proteins, i.e., by direct oxidation by oxygen. See Wu, paragraph [0098]. Based on the teachings of Wu, a person of skill in the art would only be motivated to use inhibitors of direct oxidation by oxygen to improve the stability of an adenovirus formulation. Based on these teachings, a person of skill in the art would not be motivated to substitute an inhibitor of metal-ion catalyzed free radical oxidation for an inhibitor of direct oxidation with oxygen. EDTA and ethanol only inhibit metal-ion catalyzed free radical oxidation and do not inhibit oxidation by

oxygen gas. Thus, Wu and Evans, either alone or in combination, do not provide any suggestion or motivation for a virus formulation comprising an EDTA/ethanol combination.

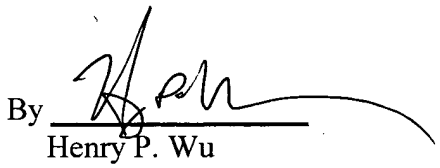
The rejection also fails to address the limitation in dependent claims, such as those claims providing for histidine in combination with Tris buffer. Wu merely indicates the use of histidine as a buffer. See Wu, paragraph [0031]. The present invention includes descriptions illustrating the ability of histidine to increase adenovirus stability, and provides embodiments where histidine is included with a buffer such as Tris.

For the above reasons, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. 103.

CONCLUSION

Applicants believe the claims are in condition for allowance. An early indication of the same is requested. The Examiner is invited to contact Applicants' Attorney at the telephone number given below, if such would expedite the allowance of this application.

Respectfully submitted,

By 

Henry P. Wu
Reg. No. 44,412
Attorney for Applicants

Merck & Co., Inc.
P.O. Box 2000
Rahway, NJ 07065-0907
(732) 594-5312